folkehelseinstituttet
Norwegian Institute of Public Health
National Influenza Centre, Oslo
Department of Influenza
Norwegian Institute of Public Health
P.O. Box 4404 Nydalen
N-0403 Oslo, NORWAY
Tel: (+47) 21 07 65 20
Fax: (+47) 21 07 64 47
e-mail: NIC-Norway@fhi.no
www.fhi.no/influensa

NORWAY:
National Influenza Centre

Influenza Epidemiological Information prepared for the WHO Informal Meeting on Strain Composition for Inactivated Influenza Vaccines for use in the Season 2017-18 Geneva, February 2017

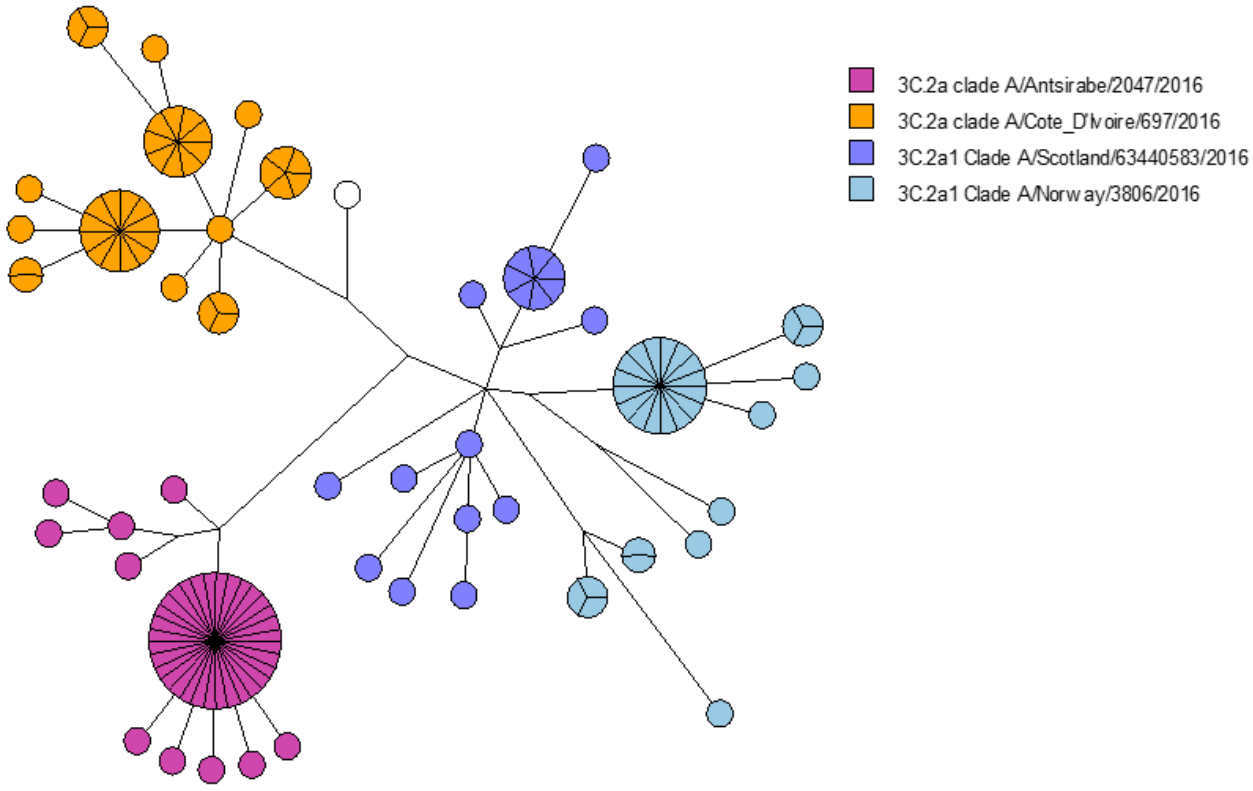


Figure 1: Maximum parsimony cluster analysis showing the different genetic clades and subclades of H3N2 viruses circulating in Norway season 2016/17. The 2016/17 H3 vaccine component is indicated with an empty circle.

Contents

1: The 2016-2017 influenza season, Norway

Summary

- In many parts of Norway the influenza season had an unusually early start and peaked around New Year
  - Only the 2009 (pandemic) and 2003/04 (Fujian strain) peaks occurred earlier during last 20 years
- Some parts had a slower developing outbreak and may still be on the increase
- The early peak in all-country ILI incidence indicated medium intensity
- There is strong (~ 95%) predominance of influenza A(H3N2), with very few A(H1N1)pdm09 viruses reported
- As in other A(H3N2)-dominated seasons, the elderly are particularly affected.
- In contrast to most other countries in Europe, the A(H3N2) viruses in genetic clade 3C.2a are in majority in Norway, with only a minority in sub-clade 3C.2a1
- 3C.2a subclade A/Antsirabe/2047/2016 viruses were more prominent in elderly and hospitalised patients.
- Influenza B viruses play a very minor role so far this season. However, both influenza B/Yamagata- and B/Victoria-lineage viruses are accumulating genetic changes, and particularly B/Victoria viruses in Norway form a distinct clade.
- As might be expected with an outbreak affecting a subpopulation with above-average vaccine coverage and a partially protective vaccine, influenza cases in vaccinated individuals are commonplace and more frequent this season than the season before.
- The incidence of laboratory-confirmed influenza hospitalisations was highest in the elderly
- Excess mortality was observed in week 50/2016 to week 3/2017, particularly in the elderly. Fatal influenza cases have also been reported from intensive care units.
- There was reduced protective antibody immunity against the H3N2 vaccine strain (A/Hong Kong/4801/14-like viruses) in August 2016 compared to the previous year. On the other hand, seroprevalence against the H1N1 vaccine strain (A/California/07/09), had risen to the highest observed since just after the influenza pandemic in 2009 (details on page 14).

A look back at the two preceding seasons

- The last H3N2 influenza outbreak in 2014/15 was of medium intensity and co-dominated by two influenza A(H3N2) genetic variants, in approximately equal numbers: the non-antigenic-drift 3C.3b group and the antigenic-drift 3C.2a group.
    - Accordingly, a proportion of the population is expected to have encountered H3N2 group 3C.2a viruses before
- The 2015/16 season was dominated by influenza A(H1N1)pdm09 viruses, mostly of the 6B.1 genetic group, and the outbreak was of medium intensity. Influenza B viruses, primarily of the B/Victoria/2/87 lineage, constituted a third of the cases and dominated towards the end of the season. Post-season predominance of A(H3N2) viruses through the summer months heralded the dominance of this virus in the present season.

Incidence of influenza-like illness

The incidence of influenza-like illness (ILI) in Norway is monitored through The Norwegian Syndromic Surveillance System (NorSSS). NorSSS is a population-based automated electronic system that daily provides data from all GPs and emergency clinics in primary health care in Norway. The Department of Influenza at the Norwegian Institute of Public Health (NIPH) receives data from the Norwegian Health Economics Administration (HELFO). NorSSS has been in operation since 2014 and is supported by retrospective data from the 2006-07 season and onwards.

The ILI consultation rate began to rise in week 45/2016, a few weeks after a marked increase in lab confirmed cases, and the epidemic threshold was reached in week 49. The peak came in week 52, which is considerably earlier than in the 5 previous seasons (Fig. 2, left). The clinical influenza activity was then at a medium level for the first time this season (Fig.2, right). In week 4/2017 the influenza activity returned to low intensity. Nine outbreaks in health care institutions have been reported since the start of the season.

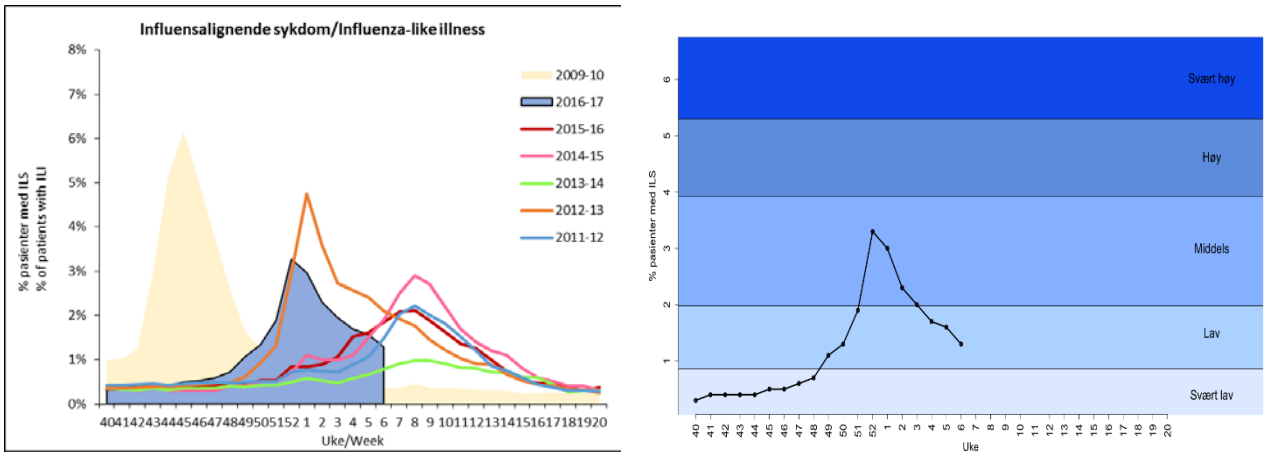


Figure 2: Weekly incidence of ILI, Norway 2016-2017.
Proportion of patients in general practice and emergency clinics presenting with ILI, by calendar week. In the left-hand panel a selection of previous seasons is also shown. In the right-hand panel, the ILI incidence is shown against the present-season MEM intensity thresholds

Virological surveillance.

A network of volunteer sentinel physicians throughout the country collects specimens from patients with ILI for analysis at the National Influenza Centre. In addition, medical microbiology laboratories that perform influenza diagnostics weekly report the number of positives and the number of specimens tested, and also contribute positive specimens to the NIC for further characterisation. Even though most of these laboratories are in hospitals, the majority of specimens tested for influenza virus tend to be from outpatients attending general practitioners.

Sporadic cases of laboratory verified influenza were recorded weekly throughout the summer and early autumn 2016 (cf. our report for the September 2016 VCM). A clear increase in the numbers was noticed from early November onwards and already then gave indication of an early developing outbreak compared to previous seasons (Figure 3, table 1). From the outset, influenza A(H3N2) viruses were clearly predominating. The number of weekly detections crossed the 1000 mark in early December and the all-laboratories positivity rate exceeded 20 per cent during the peak weeks 50/2016 through 1/2017. The subsequent decline has been slower than the pre-Christmas rise, and in some parts of the country the activity peaked several weeks after others; in some cases it may not yet have culminated.

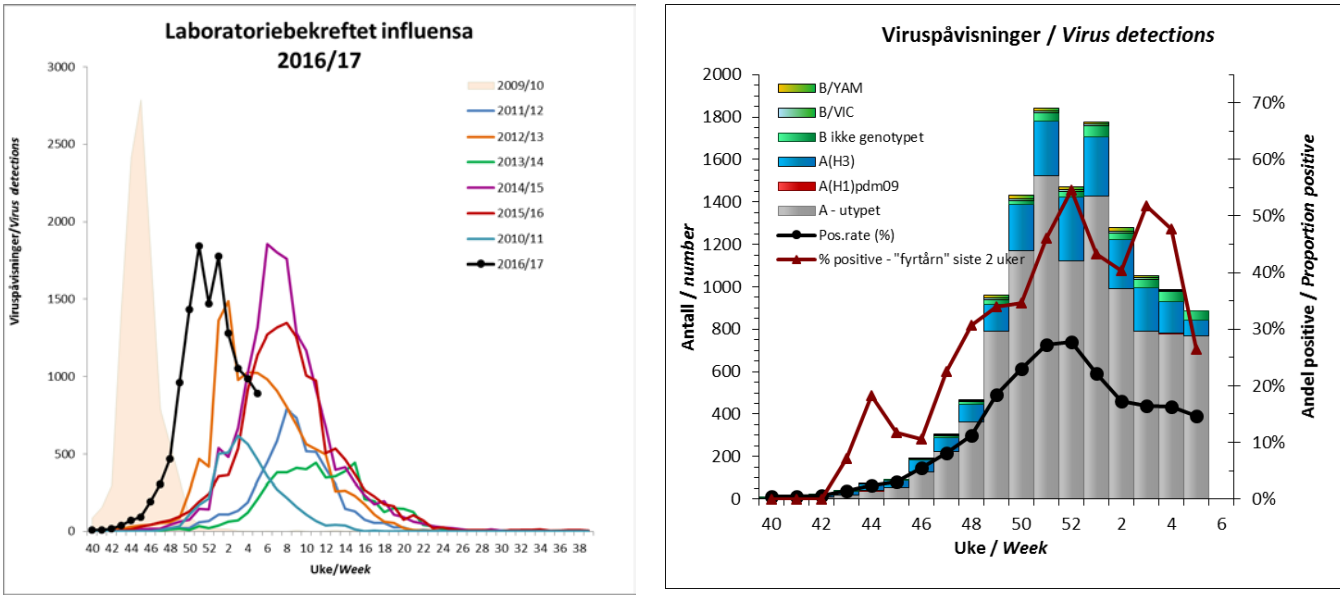


Figure 3: Laboratory detections, Norway 2016-2017. Left hand panel: Weekly numbers of influenza virus detections, with previous season numbers shown for comparison. Right hand panel: Weekly number of the different influenza viruses is displayed as stacked bars, and influenza virus positivity rates of sentinel specimens ("fyrtårn") and all lab testing, respectively, are shown as line graphs.

By week 5 more than 85 000 samples had been analysed for influenza at Norwegian medical microbiology laboratories this season (Figure 4). Among all reported influenza virus infections, 96% have been type A and 4% type B (figure 5). A(H3N2) constitutes more than 99 % of the subtyped type A viruses, with very few (17 out of 2209) A(H1N1)pdm09 viruses. Among genotyped type B viruses, proportions are very different between localities, with Yamagata/16/88-lineage viruses in slight majority (59%) across the country.

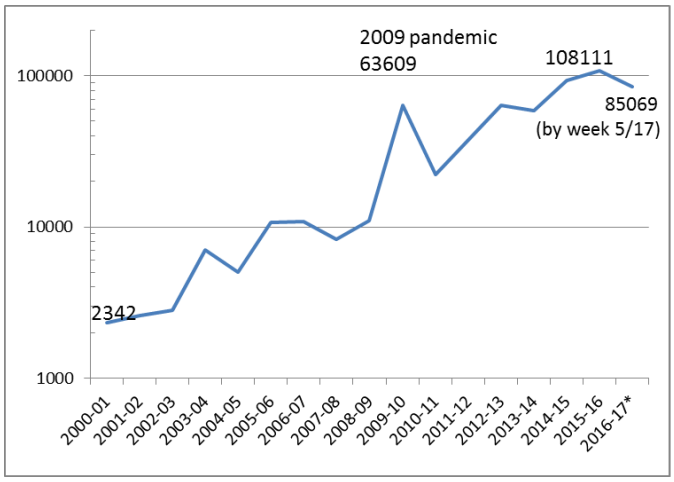
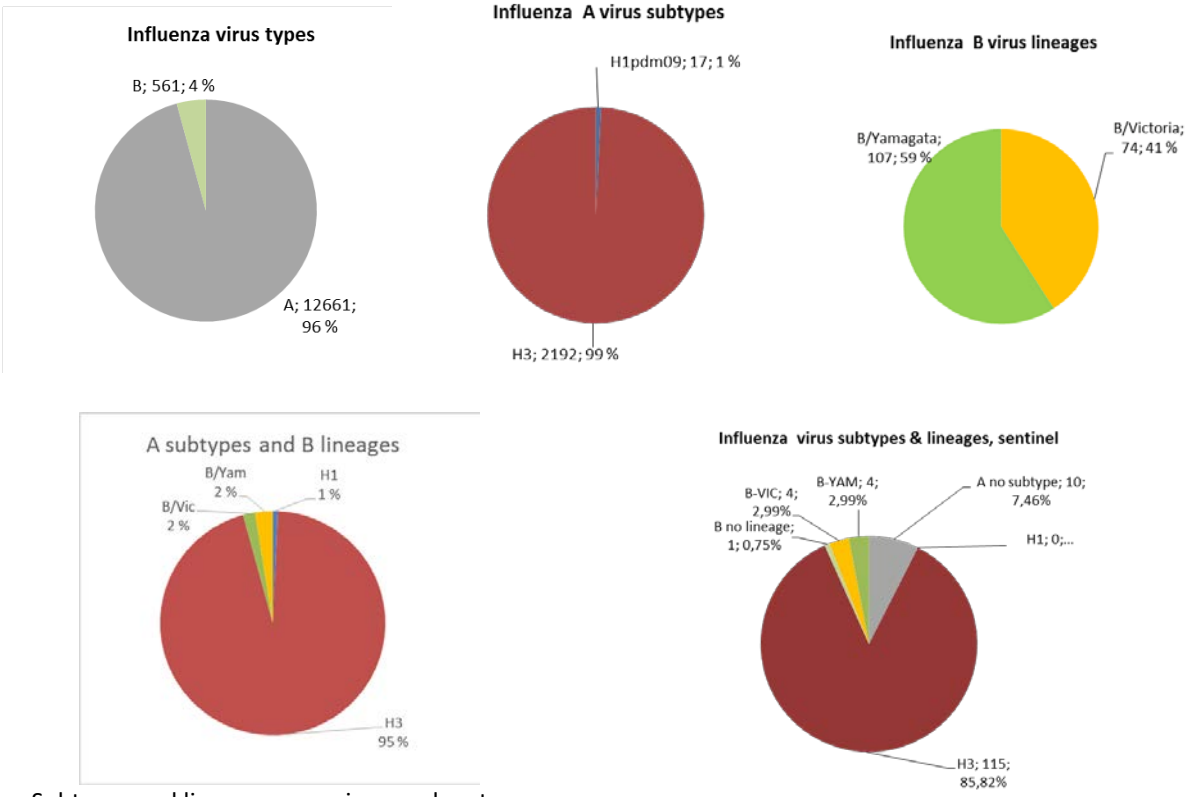


Figure 4. Number of tests for influenza virus carried out in Norwegian medical microbiology laboratories, as recorded in weekly reports to the NIC (*current-season total is incomplete).



Subtypes and lineages, superimposed on type distribution

Figure 5. Proportions of 2016/17 season influenza virus subtypes and lineages among viruses analysed in Norway, by 14th of February 2017. For comparison, all-laboratories proportions of A/B type, A subtypes and B lineages are shown in the upper row. The subtype and lineage frequencies are superimposed on type distributions in the lower left panel, for comparison with the distribution among sentinel specimen data. The relative frequencies are generally consistent. The proportion of the H1 subtype may be overestimated in the all-laboratories data because more than three times more viruses have been tested for H1 than for H3. Sentinel data are not biased in this way but the numbers are more limited.

Table 1: Proportion of specimens positive for influenza virus, influenza virus detections per type/subtype/lineage (sentinel plus non-sentinel), and weekly incidence of influenza-like illness, in Norway from week 40/2016 through week 5/2017.

	Viruspåvisninger/*Virus detections*								
UKE/ *week*	Prøver/ *Specimens*	% positive	A(utypet) *not subtyped*	A(H1) pdm09	A(H3)	B ikke genotypet *not lineage typed*	B/ Victoria lineage	B/ Yamagata lineage	ILI % consultation rate
40	2274	0.4 %	5	0	2	1	0	0	0.3 %
41	2419	0.4 %	1	0	7	1	0	0	0.4 %
42	2686	0.6 %	9	0	7	1	0	0	0.4 %
43	2706	1.4 %	18	0	19	1	0	0	0.4 %
44	3000	2.4 %	35	3	33	1	1	0	0.4 %
45	3080	3.0 %	52	3	33	5	0	0	0.5 %
46	3500	5.5 %	126	2	55	6	1	1	0.5 %
47	3725	8.2 %	225	0	65	9	4	1	0.6 %
48	4206	11.2 %	361	2	82	15	2	7	0.7 %
49	5231	18.4 %	788	1	127	23	8	13	1.1 %
50	6248	22.9 %	1170	1	216	20	9	17	1.3 %
51	6772	27.2 %	1522	0	260	39	9	11	1.9 %
52	5286	27.8 %	1121	0	301	26	9	14	3.3 %
1	8017	22.2 %	1427	0	280	51	10	8	3.0 %
2	7420	17.2 %	981	1	242	28	9	18	2.3 %
3	6402	16.5 %	783	1	209	42	7	12	2.0 %
4	6038	16.3 %	774	2	155	46	5	5	1.7 %
5	6056	14.7 %	768	1	75	44	0	0	1.6 %
Total	85066		10166	17	2192	359	74	107	
UKE/ *week*	Prøver/ *Specimens*	% positive	A(utypet) *not subtyped*	A(H1) pdm09	A(H3)	B ikke genotypet *not lineage typed*	B/ Victoria lineage	B/ Yamagata lineage	
		Type A:	12375		Type B:	540			

Pre-season seroprevalence and age-distribution of viruses detected in 2016-17 season.

In figure 6, the pre-season population immunity within age groups against the different influenza viruses, described in section 3, is shown together with the in-season occurrence of infections for the corresponding viruses and age groups, displayed as incidence of laboratory verified cases.

Figure 6. Prevalence of protective antibody to various influenza viruses in August 2016 (% seropositive, bars) and the age distribution of the different influenza viruses in the 2016/2017 influenza season (up to week 6/2017, incidence per 10^4 population, line plot).

Since the number of viruses subjected to type, subtype and variant testing differs widely, the incidences are comparable between age groups in the same panel, but incidences are not comparable between the panels. The age profiles of immunity, as well as of infection, are very different between the different subtypes and lineages.

Particularly in the children and young adults, there is a good correspondence between high pre-season seroprevalence and suppressed incidence of infection for A(H1N1) and A(H3N2). Although the number of laboratory verified H1N1 cases is very low, the profile corresponds well to the incidence age pattern seen last winter. This is the case also for the H3N2, B/Yam and B/Vic viruses (cf. our report for the September 2016 VCM).

For other age segments and for the influenza B lineages, seroprevalence does not predict the relative in-season incidences so well this season.

Surveillance of laboratory-confirmed influenza in hospitalised patients

In the laboratory-based surveillance system of influenza-confirmed hospitalisation, seven microbiological hospital laboratories participate. These laboratories cover approximately 50% of the Norwegian population, and report each week the number of influenza virus detections in hospitalised patients (all wards) according to influenza type (A, B) and age group. From week 40/2016 and until week 5/2017 influenza virus has been detected in 1990 hospitalised patients. The number hospitalisations increased gradually from week 45, peaked in week 52, decreased from week 1 to week 2 and stabilised from week 3 to week 5 (Figure 7). Most patients hospitalised with influenza have been 60 years or older (Figure 7). Influenza A virus has been the most frequently detected influenza type among the hospitalised patients (97%). This is the third year this surveillance system has been in operation. Until now this season, the cumulative number of influenza-confirmed hospitalisations is at the same level as the total number reported in the entire 2015/2016 season (n = 2067) (Figure 7).

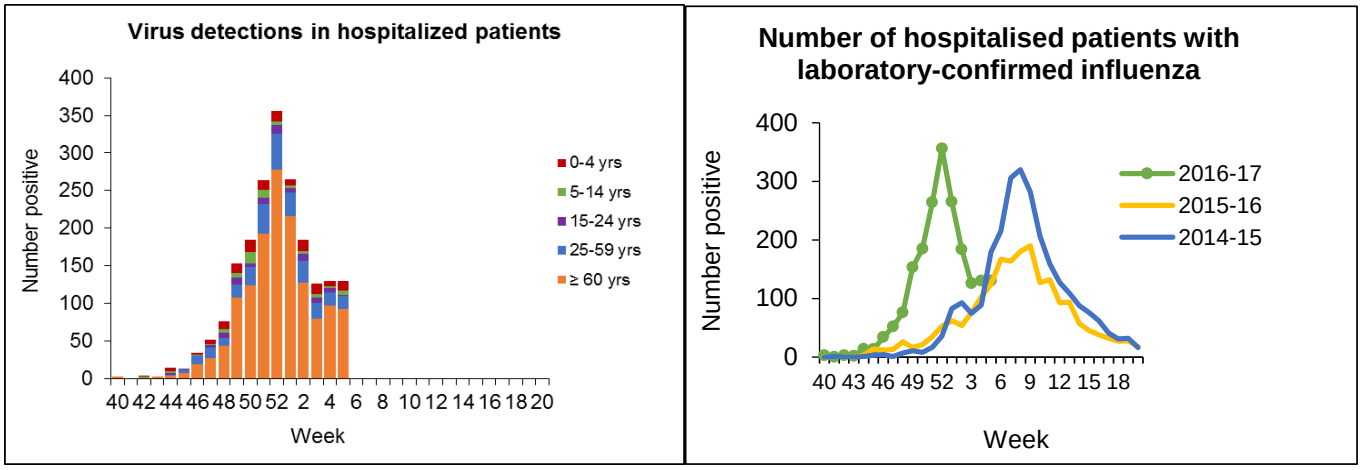


Figure 7. Left hand panel: The number of influenza virus detections in hospitalised patients per week during influenza season 2016/2017, age-distributed. Right hand panel: The number of hospitalised patients with confirmed influenza per week the three last influenza seasons. To be able to compare the seasons, week 1/2016 is the average of the number of patients hospitalised with influenza in week 53/2015 and week 1/2016.

Influenza patients in intensive care units

This season it is piloted whether the Norwegian Intensive Care Registry (NICR) can be used as a data source for a national surveillance of influenza patients in intensive care units. Almost all ICUs in Norway report data to NICR. As part of the pilot, NICR has asked all ICUs from week 46/2016 weekly to report the number of patients in ICUs with laboratory-confirmed influenza, the number of patients in ICUs with clinically suspected influenza and the number of deaths among patients with confirmed or suspected influenza admitted to ICUs (Table 2). Anonymised data are reported from NICR to the NIPH. Since this is the first season the scheme is operated, it is not possible to compare the results from this season with results from previous seasons.

Table 2. The number of confirmed or suspected influenza ICU admissions and deaths from week 46/2016 until week 5/2017.

Number of patients admitted in ICUs with laboratory-confirmed influenza	165
Number of patients admitted to ICUs with clinically suspected influenza	105
Number of deaths among patients with laboratory-confirmed or clinically suspected influenza admitted to ICUs	19

Excess all-cause mortality
The NIPH has been conducting weekly all-cause mortality surveillance since the 2015/2016 season, using the EuroMOMO algorithm. Historical data are available from 2008. This season, significant excess mortality, has been observed in Norway in six consecutive weeks (week 50/2016 to week 3/2017), particularly in the elderly (> 65 years). Excess mortality was also observed in week 52/2016 in the age group 15-64 years.
http://www.euromomo.eu/

2: Characterisation of influenza viruses circulating in Norway, 2015-16 season

Influenza A(H3N2)

As mentioned, the 2016-17 season in Norway has been dominated by H3N2 viruses (~95% of all influenza positive samples). By week 5 911 samples have been PCR-positive for H3 at the NIC Norway, 15.7% of those have been sequence analysed and HA sequences of 6.6% of all PCR-positive H3 viruses have been submitted to GISAID. Strainbased reporting of virus characterisation data was done routinely through TESSy. Both H3 viruses of genetic clades 3C.2a and its sub-clade 3C.2a1 have been circulating as during the summer months of 2016. Each clade has been represented by two genetic subgroups. The 3C.2a clade of H3 viruses has predominated in Norway and not the 3C.2a1 viruses, reported to dominate in Europe by ECDC and WHO. The 3C2.a1 viruses were mostly seen during the summer months before the onset of the 2016-17 season. The 3C.2a viruses predominated over 3C.2a1 viruses in the beginning of the season and in the recent weeks (report made from data from week 5).

The main group of viruses within the genetic 3C.2a clade are most closely related to the reference virus A/Antsirabe/2047/2016. In addition to the N121 and N171 amino acids, the Norwegian group of viruses possess the T131K, R142K and R261Q substitutions (in reference to A/Texas/50/2012). Both T131K and R142K are in antigenic site A and have been related to antigenic drift. In the south-eastern part of Norway and in mid-Norway H3 cases increased rapidly very early in the season (week 43) and these mutated viruses caused most outbreaks driving this rapid increase. Based on the phylogeny this subclade could be considered for a new clade name.

The other genetic subgroup of 3C.2a viruses circulating in Norway this season resembles the A/Cote D'lvoire/697/2016 reference virus with the N121K and R144K substitutions, some of the Norwegian viruses possessed the F219Y substitution in addition. Most Norwegian 3C.2a1 viruses possessed the I140M substitution, but a smaller group of these viruses possessed N142G. Very few 3C.2a1 viruses possessed K92R and Q311 (see phylogeny section).

Although data are relatively few and biased by sampling strategy there is an indication that the Antsirabe-subclade viruses are slightly overrepresented among hospitalised patients (Figure 8). The proportion of these viruses is also slightly higher in the elderly (Figure 11). The elderly have been more exposed this season and hospitalised than other age groups (cf. section on hospitalisations)

There has been little change in the distribution of H3 viruses with regard to genetic subclades from the beginning of the season and into the current mid-season. Possibly, there are slightly more Antsirabe-subclade 3C.2a viruses at present time, week 5 (Figure 9).

The Norwegian Antsirabe-subclade viruses in the 3C.2a clade share NA genes with the 3C.2a1 viruses, while the Cote_D'lvoire-subclade 3C.2a viruses define a separate clade of NA genes (see phylogeny section). One could speculate that the 3C.2a1 neuraminidase together with the Antsirabe 3C.2a HA improves viral fitness, causing its rapid spread in Norway.

From week 40 to week 5, 52 influenza H3 viruses (5% of H3 viruses received at NIC Norway), both virus isolates and clinical samples, have been shipped to the WHO Collaborating Centre for Reference and Research on Influenza, Crick Worldwide Influenza Centre.

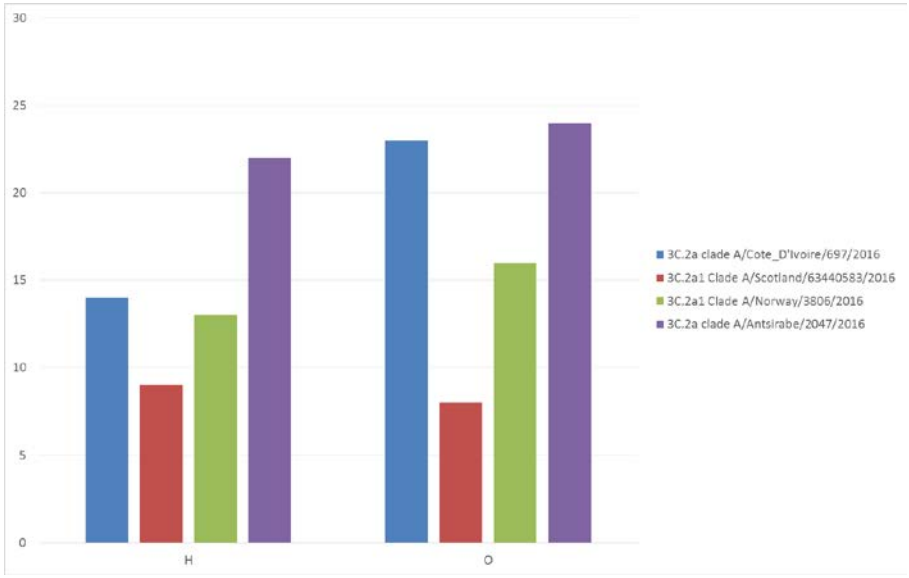


Figure 8: H3 clade distribution in hospitalised patients vs. outpatients

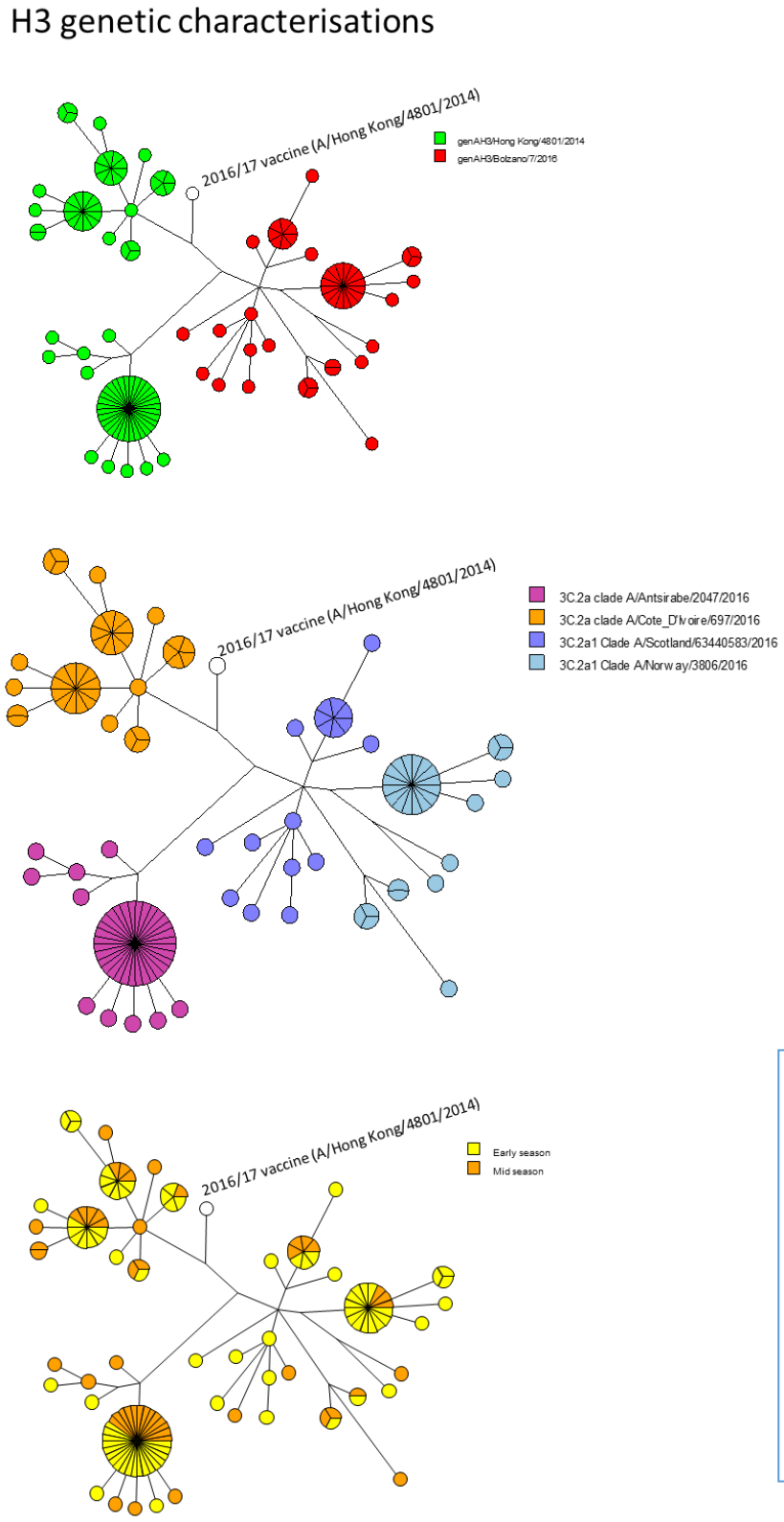
Neuraminidase activity analysis of the NA genes from the different H3N2 viruses could indicate that the 3C.2a group of viruses had more efficient NA activity than the 3C.2a1 viruses. All H3 viruses react poorly in the HA assay (Table 3).

Table 3: HA and NA activity by different H3 clades; mean dilution to standardise NA activity ; and mean HA titre

3C.2a subgroups	Mean dilution for IC50*	Mean HA titre
3C.2a clade A/Antsirabe/2047/2016	53	1
3C.2a clade A/Cote_D'Ivoire/697/2016	61	2
3C.2a1 Clade A/Norway/3806/2016	34	3
3C.2a1 Clade A/Scotland/63440583/2016	38	2

*Mean dilution for IC50 value indicates the dilution factor needed to adjust/standardise the neuraminidase activity of the virus to 15500 RFU. Higher value indicates a virus with higher neuraminidase activity.
HA titer is a measure of haemagglutination activity.

Figure 9: Cluster analysis of H3 viruses circulating in Norway



Cluster analysis of HA H3 viruses in Norway compared to the 2016/17 H3 vaccine component A/Hong Kong/4801/2014 (white circle). Maximum parsimony analysis of the first 770b of the HA genes. Upper figure shows clustering in regard to the defined genetic clades. Middle figure shows clustering in regard to subclades within the defined genetic clades. Lower figure shows viruses from the beginning of the season (yellow, week40-50) and mid season (orange, week 51-12 (data includes up to week 5))in different clades..

H3 clade distribution of vaccinated vs. unvaccinated patients

Samples from persons vaccinated for the 2016/17 season made up 4,5% of all samples received to the NIC Norway, compared to 1.4% in the 2014/15 season and 1.2% in the 2015/16 season. Most people vaccinated in Norway are elderly and this season the elderly were overrepresented with H3 influenza. Table 4 summarises the percentage of patients vaccinated with lab confirmed influenza.

Table 4: Percentage vaccinated with lab-confirmed influenza

		Outpatients (%)			Hospitalised (%)			Season total		
Season	Dominating virus	H3	H1	B	H3	H1	B	Vaccinated with influenza (%)	Vaccinated with influenza	Lab confirmed influensa
2014-15	H3/B	1.4	1.6	0.6	1.1	0.0	0.7	0.9	22	2511
2015-16	H1/B	0.6	0.7	0.6	0.0	0.6	0.6	0.4	16	3917
2016-17 to week 5	H3	4.4	0	1.9	2.9	0.0	0.0	3.2	37	1151

The H3 viruses infecting vaccinated persons were evenly distributed among the different H3 genetic clades (Figure 10).

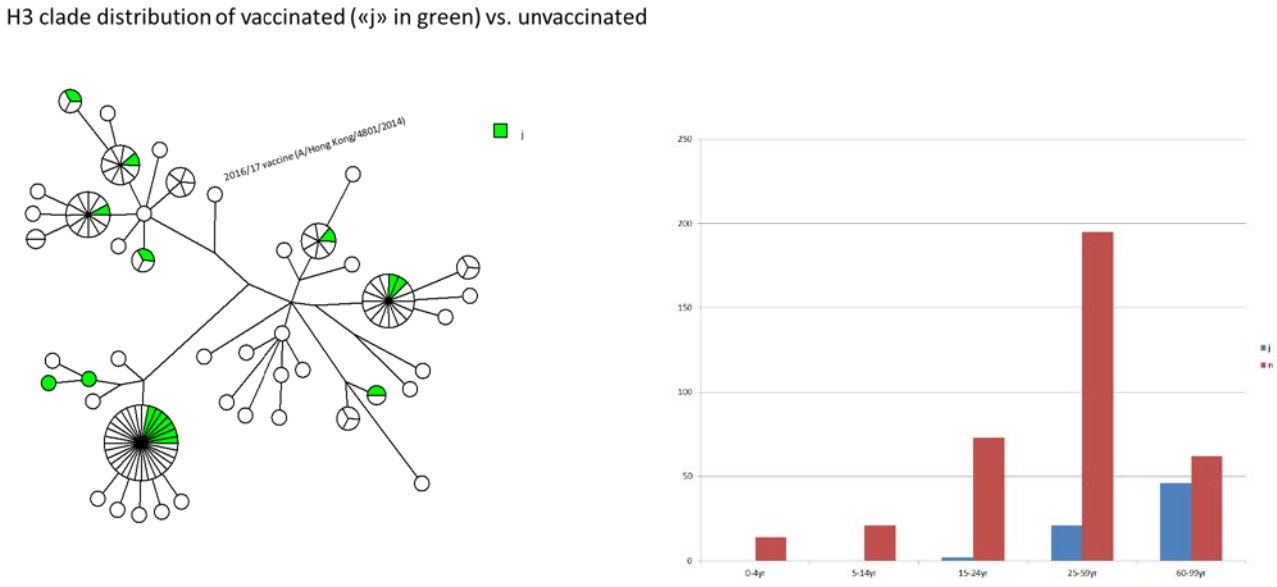


Figure 10: H3 clade (left panel) and age (right panel) distribution of vaccinated vs. unvaccinated (j=vaccinated)

The H3 3C.2a Antsirabe-subclade viruses might be slightly overrepresented in the age group 60-99 (Figure 11)

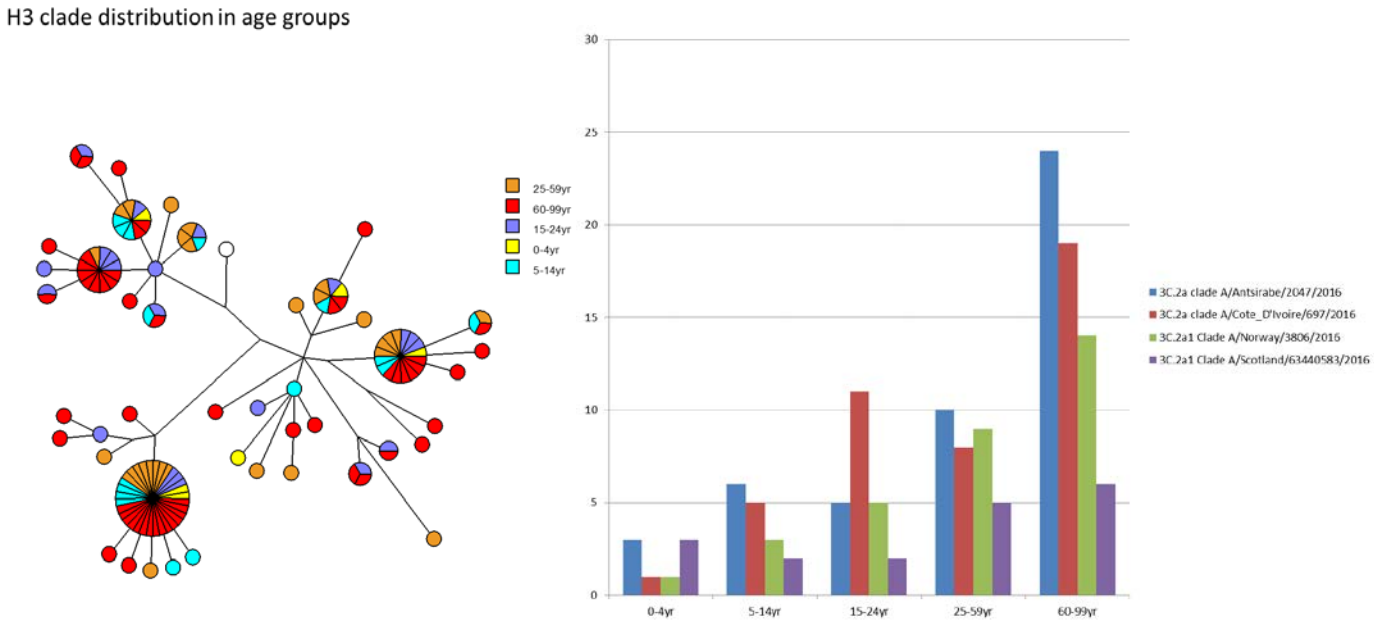


Figure 11: H3 clade distribution in different age groups

Influenza B

B/Yamagata/16/1988 lineage

Out of 129 samples PCR positive for B/Yamagata at the NIC Norway, 10% have so far been sequence analysed and HA sequences of 10,2% of all PCR-positive influenza B viruses have been submitted to GISAID. All B/Yamagata viruses from this season in Norway belonged to the genetic clade 3. Two subgroups of influenza B/Yamagata viruses circulated this season, one possessing the M251V substitution and one that in addition possessed K211R and D232N. The D232N substitution creates one additional glycosylation site in HA (see phylogeny section).

From week 40 to week 5, seven influenza B/Yamagata viruses (5% of B/Yamagata viruses received at NIC Norway), both virus isolates and clinical samples, have been shipped to the WHO Collaborating Centre for Reference and Research on Influenza, Crick Worldwide Influenza Centre.

B/Victoria/2/1987 lineage

Out of 78 samples PCR positive for B/Victoria at the NIC Norway, 17% have so far been sequence analysed. There is one main drifted group of the influenza B/Victoria viruses circulating in Norway. This group of viruses possessed the substitutions R80K and T258P. These viruses formed a subgroup to other B/Victoria viruses with no reference strain representing the clade. It is not clear, if this group of viruses should be assigned as group 1A viruses or if they should be assigned as s new subgroup.
Two viruses from the beginning of the season grouped together with the B/Ghana/DIL-16-0740/2016 reference strain characterised by the P31S substitution. I addition these two viruses also possessed N11S (see phylogeny section).

From week 40 to week 5, four influenza B/Victoria viruses (5% of B/Victoria viruses received at NIC Norway), both virus isolates and clinical samples, have been shipped to the WHO Collaborating Centre for Reference and Research on Influenza, Crick Worldwide Influenza Centre.

Influenza A(H1N1)pdm09

Few H1 viruses have circulated in Norway this season, 9 have been PCR positive for H1N1 at the NIC Norway and 5 of these have been sequence analysed (56%) and HA sequences of 44% of all PCR-positive H1 viruses have been submitted to GISAID. Strainbased reporting of virus characterisation data was done routinely through TESSy. These H1 samples clustered together genetically with the A/Slovenia/2903/2015 6B.1 group of viruses. Most H1 viruses from Norway possessed the HA substitution H51N (see phylogeny section).

From week 40 to week 5, five influenza H1N1 viruses (55% of H1N1 viruses received at NIC Norway), both virus isolates and clinical samples, have been shipped to the WHO Collaborating Centre for Reference and Research on Influenza, Crick Worldwide Influenza Centre.

Antiviral resistance monitoring

Monitoring of antiviral susceptibility has not revealed any resistance in Norwegian viruses this season.

Table 5. Norwegian influenza viruses resistant to M2 blockers (adamantanes) and the neuramidase inhibitors oseltamivir and zanamivir, during the period from week 40/2016 through week 6/2017.

pr. 15/02-17	Oseltamivir (Tamiflu®)		Zanamivir (Relenza®)		Adamantanes* (Amantadin, Rimantadin)	
Virus	Tested	Oseltamivir-resistant viruses	Tested	Zanamivir-resistant viruses	Tested	Adamantan-resistant viruses
H3	106	0 / (0 %)	106	0 / (0 %)	0	
B	18	0 / (0 %)	18	0 / (0 %)		
H1pdm09	4	0 / (0 %)	4	0 / (0 %)	0	

Two screening tools were used to determine oseltamivir/zanamivir susceptibility: sequence analysis of viral genes or a fluorescence-based neuraminidase inhibition assay.

* we have not tested for adamantane resistance in the 2016/17 season

3: Seroepidemiology Data, August 2016

The National Seroepidemiological Influenza Programme for the year 2016 analysed a total of 2028 serum samples collected during the weeks 31-35 from clinical/microbiological laboratories covering the 18 of 19 counties of Norway. The anonymised convenience sera are aiming to be representative of the Norwegian population geographically and by age composition.

The 2016 serum panel was tested by haemagglutination-inhibition (HI) against the 2016/17 seasonal influenza vaccine strains (trivalent/quadrivalent) (Table 1), i.e. A/California/07/2009(H1N1pdm09, the vaccine virus X-179A was used), A/Hong Kong/5738/14 (a H3N2/A/Hong Kong/4801/14 (3C.2a)-like reference virus), B/Brisbane/60/08 (B/Victoria-lineage 1A-like virus), and B/Phuket/3073/13 (B/Yamagata-lineage 3-like virus). Two additional viruses were also included in the analyses: The recent H1N1 virus isolate A/Slovenia/2903/15 (a H1N1 B/Michigan/45/15 6B.1-like virus, the H1 component of the 2017 southern hemisphere influenza vaccine) and A/Switzerland/9715293/13 (a H3N2 3C.3a-like virus, the H3 component of the 2015/16 season influenza vaccine). HI titres ≥ 40 against the influenza A strains and ≥80 against ether-treated influenza B strains were considered as protective levels and recorded as seropositive in this analysis. The results are shown in Table 6 and Figure 12.

Summary of outcomes

The results from the seroepidemiology study in August 2016 show that population seroprevalence to the H1N1pdm09 vaccine virus is high (46 %, 'All ages') and has increased significantly from August 2015. This is in accordance with the dominant circulation of H1N1pdm09 viruses (about 72 %) the preceding 2015/16 influenza season. The seroprevalence to the H1N1pdm09 virus in August 2016 is the highest observed since the influenza pandemic in 2009.

The previous season A(H3N2) viruses were scarce (about 7 % of circulating viruses), thus a reduced seroprevalence to H3N2 viruses were observed with the highest reduction against the A/H3N2 component of

this season's influenza vaccine (A/Hong Kong/5738/14 was used, a A/Hong Kong/4801/14 -like virus, 3C.2a genetic group). A lesser reduction was seen against the A/Switzerland/9715293/13 (3C.3a genetic group, H3 component of the previous season vaccine). The reduction in seroprevalence against A/Hong Kong virus might be due to waning immunity against this H3 variant and thus shorter duration of protective antibodies.
The seroprevalences against influenza B viruses were also reduced in most age groups, both against the B/Victoria- and the B/Yamagata-vaccine strains, B/Brisbane/60/08 and B/Phuket/3073/14 (quadrivalent vaccine only), respectively.

Influenza A(H1N1)pdm09

In August 2016 the prevalence of protective antibodies to A(H1N1)pdm09 was 46 % (All ages), an increase of 7 percentage points from August 2015. This is consistent with the high level of H1pdm09-like viruses circulating the preceding season with the pdm09 being the dominant virus (72 %). A similar pattern was seen for the various age groups (Table 1, Figure 12) with the highest increase (13 percentage points) in the 5-14 year olds. A similar increase was also seen in the other age groups (between 4 to 8 percentage points) except for those 60 year or older with no change in seroprevalence to H1pdm09 from the previous year. The serum panel was also tested against the more recent H1pdm09 reference strain A/Slovenia/2903/2015 (subgroup 6B.1). The seroprevalence to this strain is similar to the pandemic strain for 'All ages', although a somewhat higher prevalence (4 and 6 percentage points) is seen in 0-4 and 15-24 year olds, respectively, while for the 60+ year olds there was a reduced seroprevalence by 3 percentage points.

Normalization/adjustment of HI-titres to A(H1N1)pdm09. In August 2016 and the previous years 2011 to 2015 the serum panels were tested against the reassortant vaccine strain X-179A (A/California/07/09). The resulting HI titres with X-179A vaccine virus have been adjusted to the A/California/07/09 wild type virus using an international standard serum to A(H1N1)pdm09 (IS10/202). The normalized/adjusted results are compared to the HI results from previous years as indicated (Table 1).

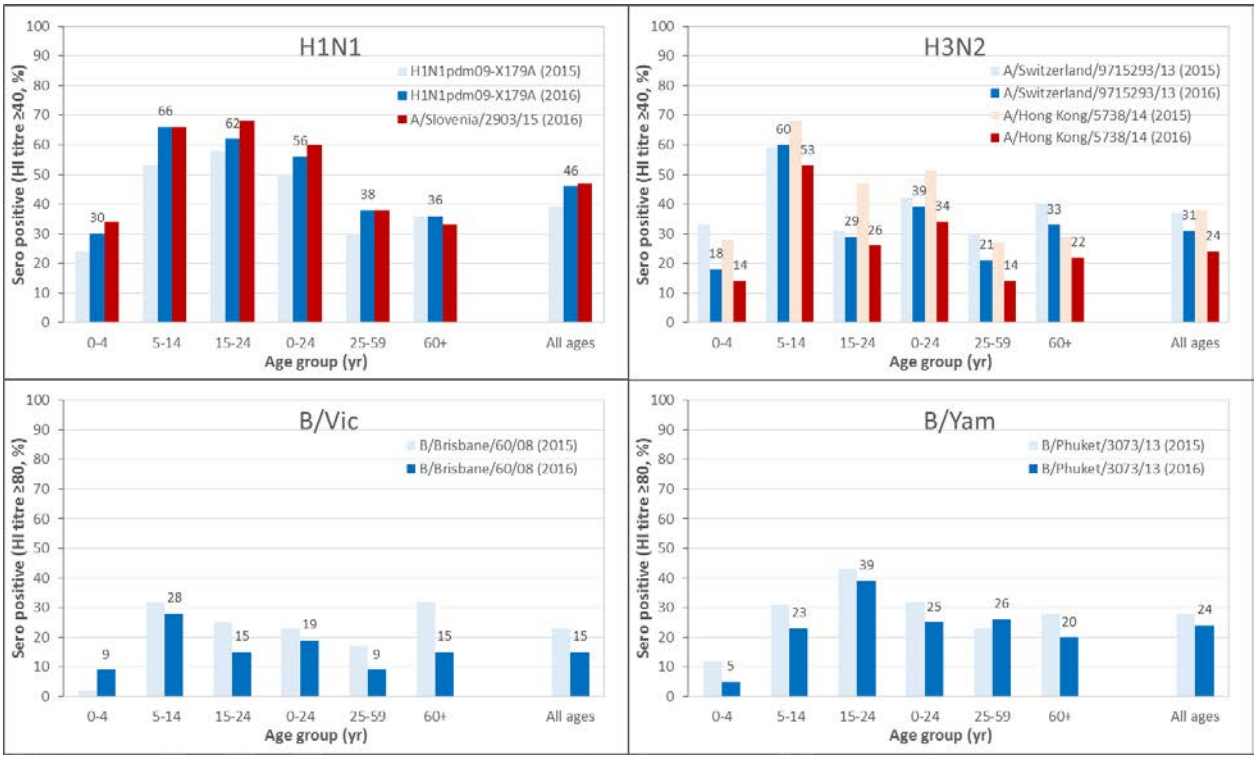


Figure 12. Seroprevalence in August 2016 against current influenza A and B reference and vaccine strains in various age groups. For comparison the seroprevalence against some virus strains in August 2015 are also shown. Columns in dark colour (blue, red) show the seroprevalence in 2016. Columns in light blue and pink colour show the corresponding seroprevalences in 2015 for some strains. Further details are given in the text

Influenza A(H3N2)

The seroprevalence in August 2016 against the current H3N2 vaccine strain (A/Hong Kong/4801/14, 3C.2a genetic group, represented by A/Hong Kong/5738/14), as well as the seroprevalence against the vaccine strain of the 2015/16 season (Switzerland/9715293/2013, 3C.3a genetic group virus), are reduced compared to the previous season, from 38 % to 24 % and from 37 % to 31 % for 'All ages', respectively. A reduced seroprevalence is seen in most age groups, the highest reduction in those 15-24 year old (by 21 percentage points), while a reduced seroprevalence by 13 to 17 percentage points is seen in the other age groups, except for those 60 year and older with less reduced seroprevalence against the H3N2 vaccine virus strain (by 7 percentage points). (Table 6, Figure 12). This is consistent with the low proportion of H3N2 viruses circulating the preceding season, i.e. about 7 % of detected viruses. The seroprevalence in August 2016 was particularly low (14 %) for those below 5 years of age and the 25-59 age group. This reduced seroprevalence against H3N2 viruses might thus have contributed to the high number of H3N2 viruses circulating the current season.

Influenza B

For both influenza B/Victoria and B/Yamagata lineage vaccine strains, a reduced seroprevalence was seen in August 2016, i.e. for 'All ages' a reduction by 8 and 4 percentage points, respectively (Table 6). A similar reduction in seroprevalences are seen also for most age groups for both influenza B lineage viruses except for the 0-4 year olds (B/Victoria viruses) with increased seroprevalence of 7 percentage points and for 25-59 year olds (B/Yamagata viruses) a modest increase of 3 percentage points (Table 6). In particular, for the age group 60 years and above a large reduction in seroprevalence (17 percentage points) to the B/Victoria lineage vaccine virus is observed.

Table 6. Influenza Seroepidemiological results in August 2016 - Comparison between age groups.
For comparison data from studies performed for the preceding seasons 2009-2015 are also included.

Influenza strains (Year[$])	Age groups 0-4	5-14	15-24	0-24	25-59	60+	All ages
H1 California/07/09 (2009)	**0***	**1**	**12**	**5**	**2**	3	3
H1 California/07/09 (2010 Jan)	60	**65**	46	**56**	39	36	45
H1 California/07/09 (2010)	**19**	**39**	**43**	**36**	**21**	**14**	26
H1 X-179A/A(H1N1)pdm09 (2011)	26	**31**	**37**	**33**	**17**	**13**	21
H1 X-179A/A(H1N1)pdm09 (2012)	**14**	**35**	**39**	**32**	**14**	**14**	22
H1 X-179A/A(H1N1)pdm09 (2013)	**26**	**43**	**53**	**43**	**26**	**20**	32
H1 X-179A/A(H1N1)pdm09 (2014)	**27**	**52**	**58**	**49**	**31**	**30**	39
H1 X-179A/A(H1N1)pdm09 (2015)	**24**	**53**	**58**	**50**	**30**	36	39
H1 South Africa/3626/13 (2015)[1)]	35	**62**	**57**	**55**	**31**	**22**	40
H1 X-179A/A(H1N1)pdm09 (2016)*	*30*	*66*	*62*	*56*	*38*	*36*	*46*
H1 Slovenia/2903/15 (2016)	*34*	*66*	*68*	*60*	*38*	*33*	*47*
H3 Victoria/361/11 (2013)	27	57	38	43	21	29	32
H3 Texas/50/12 (2013)	28	65	38	45	22	29	34
H3 Texas/50/12 (2014)	**21**	**67**	**48**	**50**	**27**	42	40
H3 Switzerland/9715293/13 (2014)[1)]	20	**31**	**24**	26	**12**	27	21
H3 Texas/50/12 (2015)	**35**	**79**	**54**	**60**	**35**	44	47
H3 Switzerland/9715293/13 (2015)	33	**59**	**31**	**42**	**30**	40	37
H3 Hong Kong/5738/14 (2015)[1)]	28	**68**	47	**51**	**27**	**29**	38
H3 Switzerland/9715293/13 (2016)	*18*	*60*	*29*	*39*	*21*	*33*	*31*
H3 Hong Kong/5738/14 (2016)*	*14*	*53*	*26*	*34*	*14*	*22*	*24*
B/Vic Brisbane/60/08 (2010)	**3**	**7**	**6**	**6**	11	**18**	10
B/Vic Brisbane/60/08 (2011)	25	**31**	**9**	**21**	**10**	21	17
B/Vic Brisbane/60/08 (2012)	17	**18**	**8**	14	**8**	15	12
B/Vic Brisbane/60/08 (2013)	13	31	15	21	16	23	19
B/Vic Brisbane/60/08 (2014)	**4**	**20**	12	13	**10**	**21**	14
B/Vic Brisbane/60/08 (2015)[2)]	***2***	***32***	*25*	*23*	***17***	***32***	*23*
B/Vic Brisbane/60/08 (2016)*	*9*	*28*	*15*	*19*	*9*	*15*	*15*
B/Yam Wisconsin/1/10 (2013)	12	22	40	27	20	17	22
B/Yam Massachusetts/2/12 (2013)	17	31	66	42	36	29	37
B/Yam Massachusetts/2/12 (2014)	**14**	35	**60**	**41**	39	38	39
B/Yam Phuket/3073/13 (2014) [1)]	**2**	17	**39**	21	18	16	21
B/Yam Massachusetts/2/12 (2015)[3)]	**12**	**29**	**58**	38	36	33	37
B/Yam Phuket/3073/13 (2015)[3)]	**12**	31	**43**	32	**23**	28	28
B/Yam Phuket/3073/13 (2016)*	*5*	*23*	39	*25*	*26*	*20*	*24*
Sera analysed (n): 2013 Aug	202	349	356	907	786	436	2129
Sera analysed (n): 2014 Aug	201	337	354	892	790	429	2111
[1)]Sub-panel (n) of 2014 sera	89	127	109	325	251	138	714
Sera analysed (n): 2015 Aug	178	353	363	894	788	409	2091
[1)]Sub-panel (n) of 2015 sera (SA+HK)	91	145	130	366	282	156	804
[2)]Sub-panel (n) of 2015 sera (Brisb)	132	279	298	709	654	332	1695
[3)]Sub-panel (n) of 2015 sera (Mass+Phu)	75	183	209	467	462	232	1161
Sera analysed (n): 2016 Aug	188	351	333	874	745	411	2028

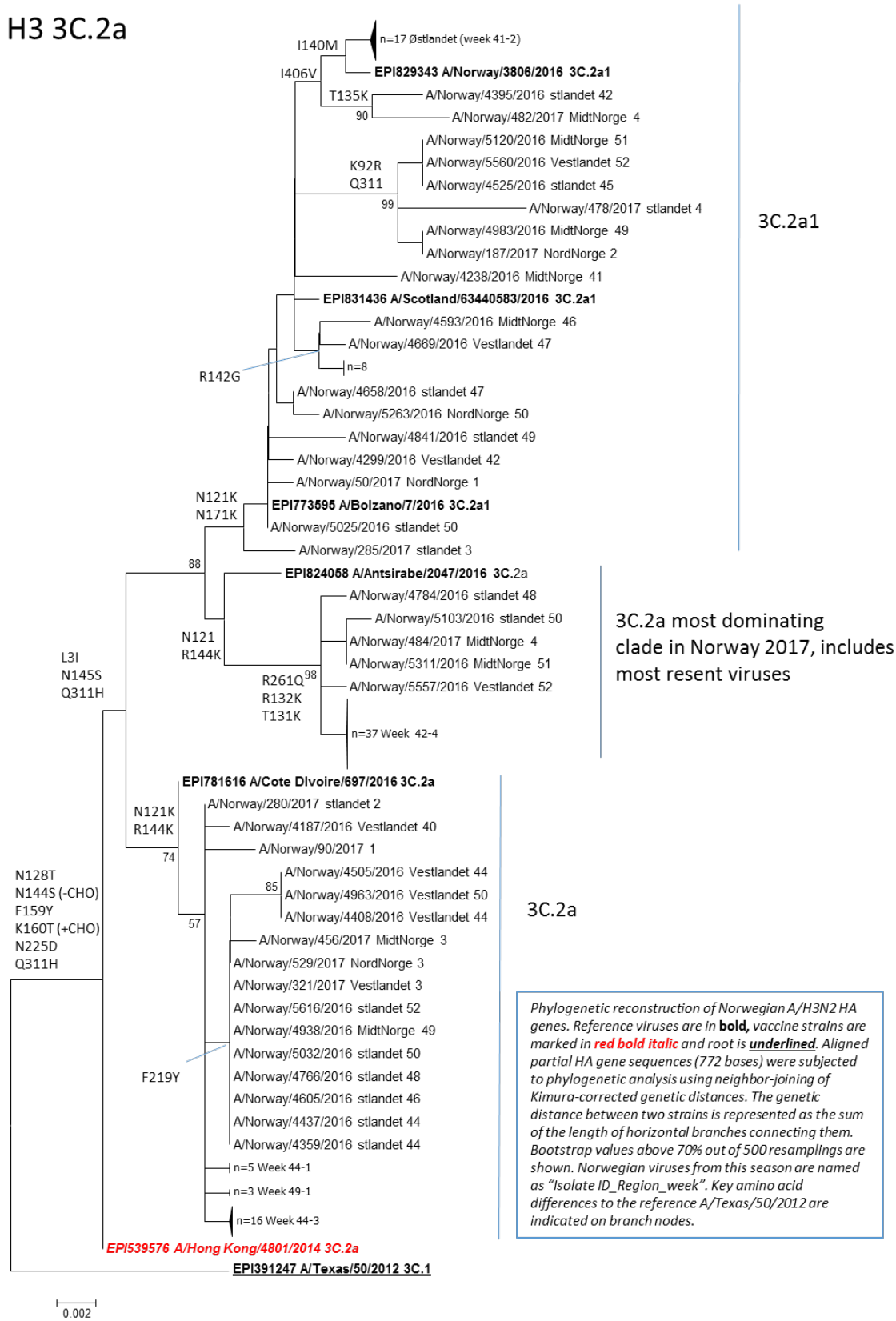
[$]Year of serum collection and HI analysis.

*All entries are per cent of sera having HI titres **≥ 40** for the A strains and **≥ 80** for the ether-treated B strains. The data given are weighted according to the age group distribution and the population density of various counties in Norway.

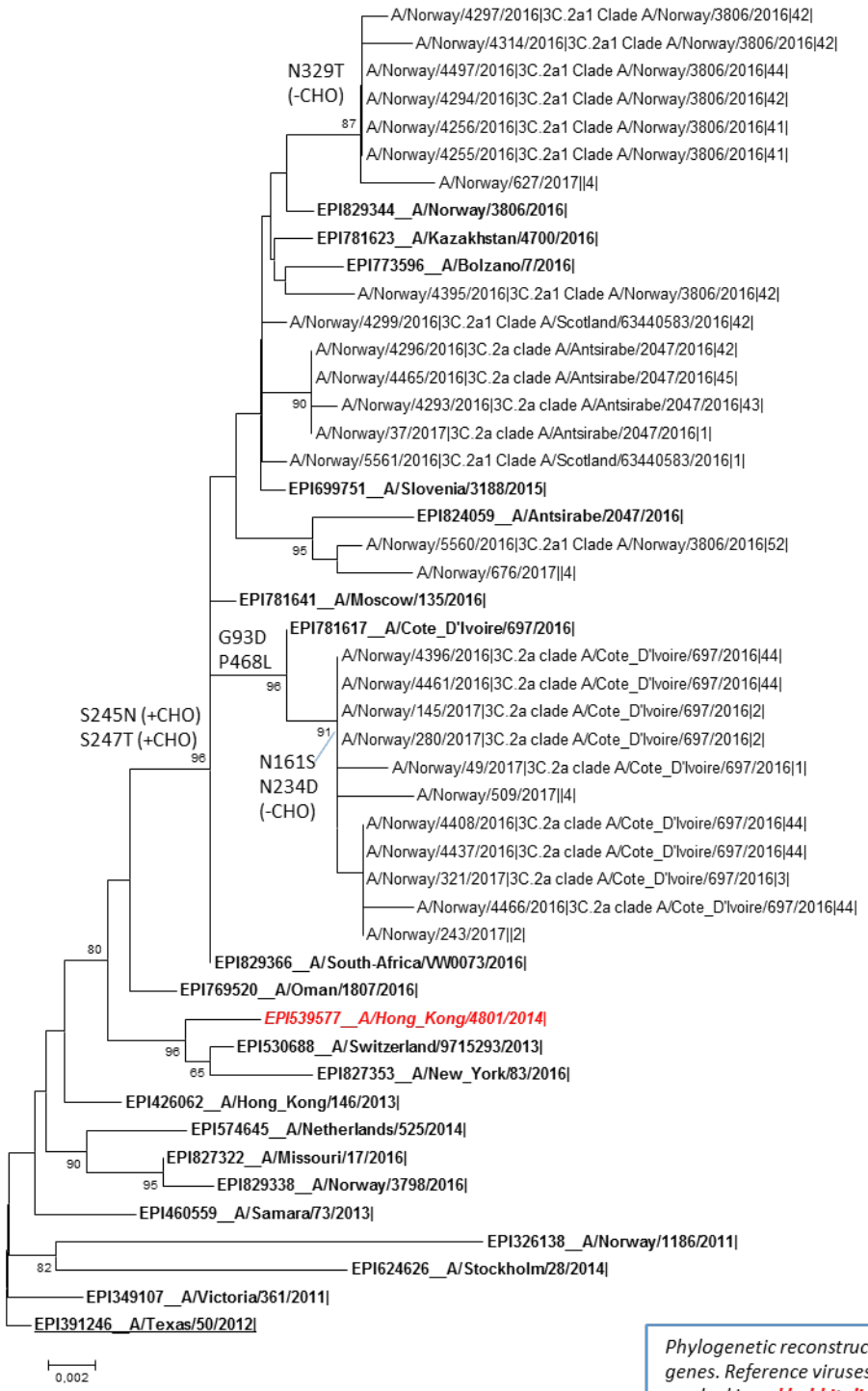
**Components of the northern hemisphere influenza vaccine (trivalent/quadrivalent) for the season 2016-2017.

B/Yam: B/Yamagata/16/1988 lineage; **B/Vic**: B/Victoria/2/1987 lineage.

4 Phylogeny: Influenza sequences, Norway 2016-17

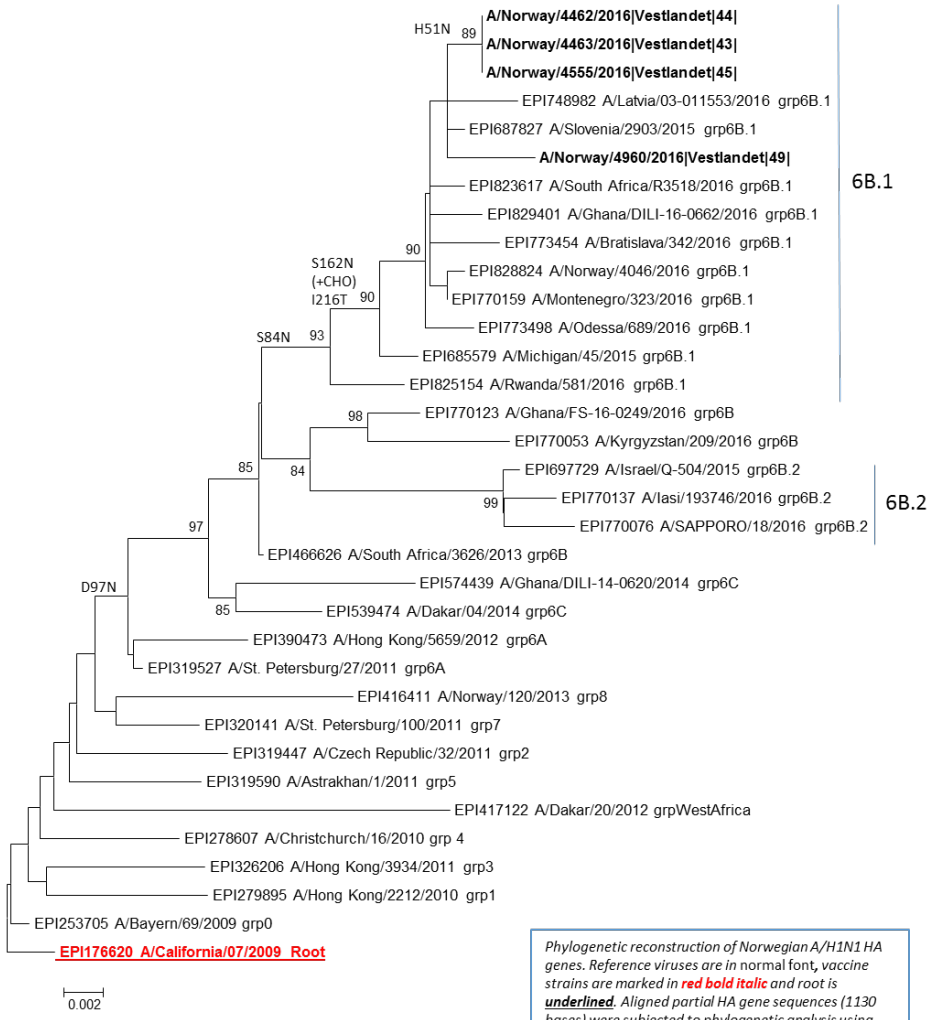


N2 3C.2a



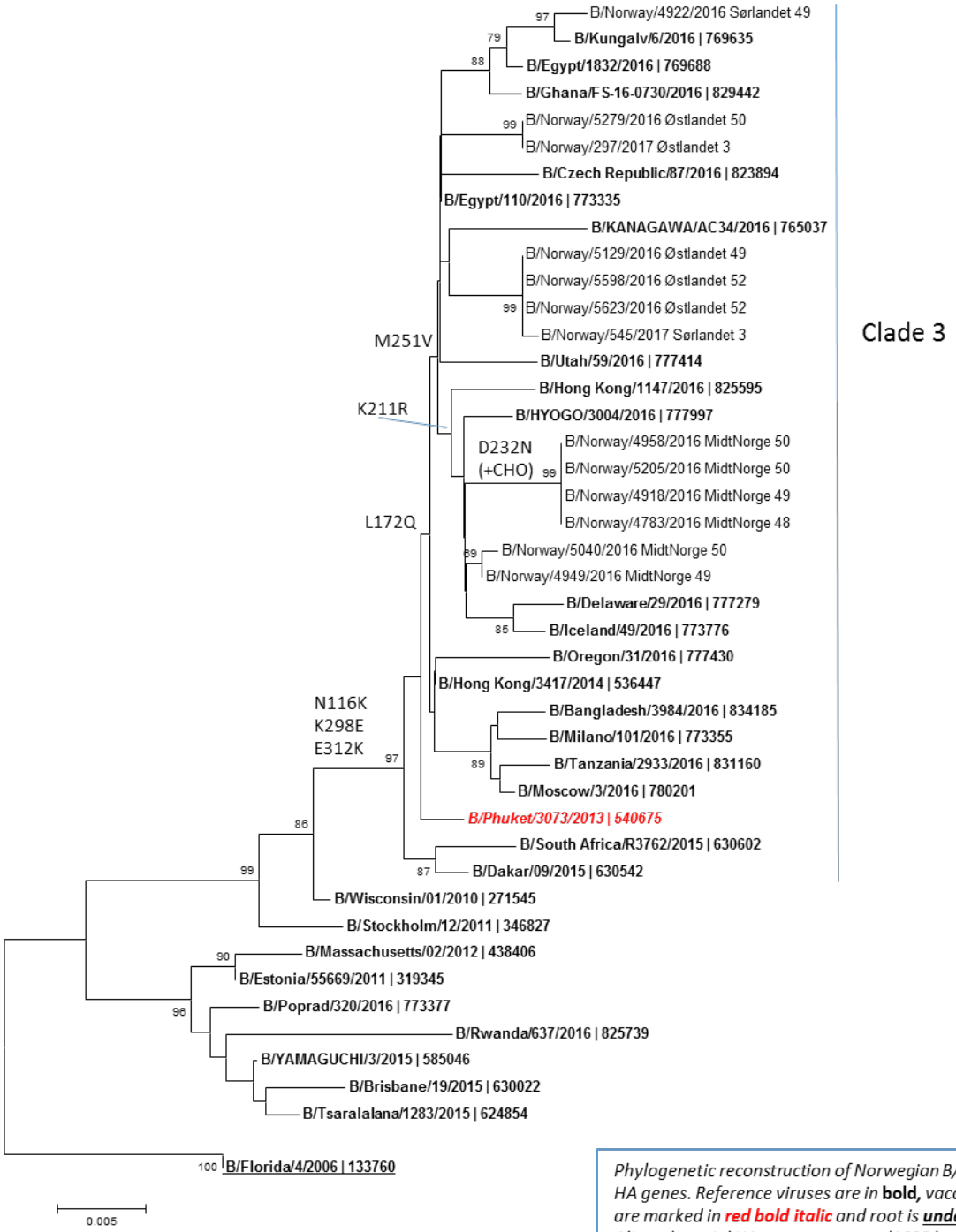
Phylogenetic reconstruction of Norwegian A/H3N2 NA genes. Reference viruses are in **bold,** *vaccine strains are marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial NA gene sequences (994 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "Isolate ID|HA genetic clade|week". Key amino acid differences to the reference A/Texas/50/2012 are indicated on key branch nodes.*

H1



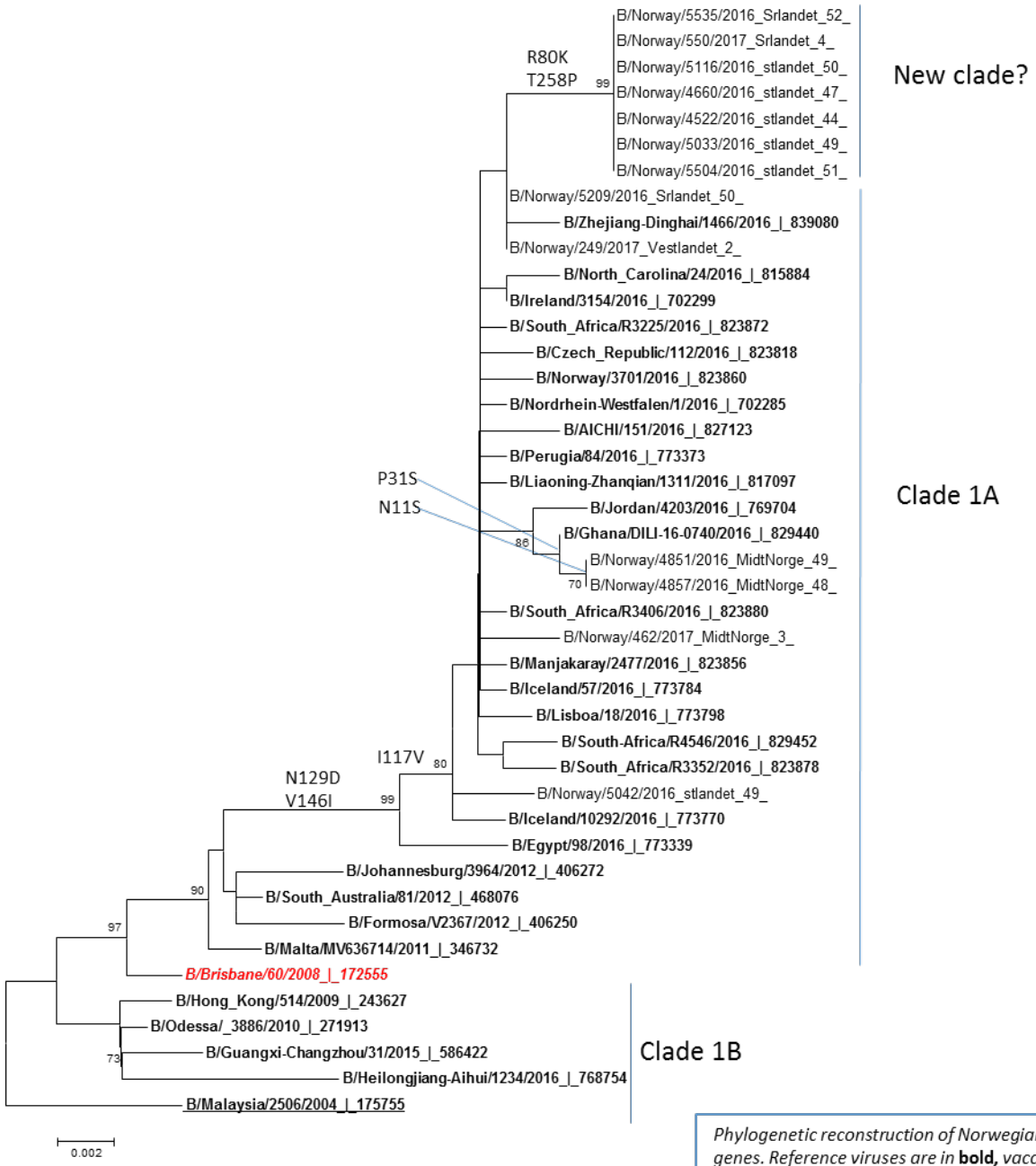
Phylogenetic reconstruction of Norwegian A/H1N1 HA genes. Reference viruses are in normal font*, vaccine strains are marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1130 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "***Isolate ID_Region_week***". Key amino acid differences to the reference A/California/07/2009 are indicated on branch nodes.*

HA B/Yamagata



Phylogenetic reconstruction of Norwegian B/Yamagata HA genes. Reference viruses are in **bold,** *vaccine strains are marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1035 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "*Isolate ID_Region_week*". Key amino acid differences to the reference B/Florida/4/2006 are indicated on key branch nodes.*

HA B/Victoria



Phylogenetic reconstruction of Norwegian B/Victoria HA genes. Reference viruses are in **bold,** *vaccine strains are marked in* ***red bold italic*** *and root is* ***underlined****. Aligned partial HA gene sequences (1050 bases) were subjected to phylogenetic analysis using neighbor-joining of Kimura-corrected genetic distances. The genetic distance between two strains is represented as the sum of the length of horizontal branches connecting them. Bootstrap values above 70% out of 500 resamplings are shown. Norwegian viruses from this season are named as "*Isolate ID_Region_week*". Key amino acid differences to the reference B/Malaysia/2506/2004 are indicated on branch nodes.*

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With best regards,
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National Influenza Centre/Department of Influenza,
Domain for Infection Control and Environmental Health,
Norwegian Institute of Public Health, Oslo, Norway

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